



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 13, 1999

MEMORANDUM

SUBJECT: **Pirimiphos-methyl.** (Chemical ID No. 108102/List B Reregistration Case No. 2535). Revised Human Health Risk Assessment and Supporting Documentation for the Reregistration Eligibility Decision Document (RED). No MRID #. DP Barcode No. D256633

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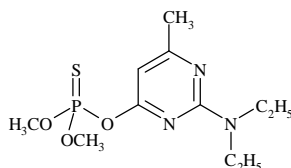
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BACKGROUND

Pirimiphos-methyl [O-(2-diethylamino-6-methyl-pyrimidinyl) O,O-dimethyl phosphorothioate] is an organophosphate (OP) insecticide belonging to the phosphorothioate subclass of organophosphates. Similar to other OPs, pirimiphos-methyl inhibits enzymes known as

cholinesterases (ChE). Pirimiphos-methyl is marketed for occupational uses only, including post-harvest control of many types of pests on stored grains/seed and fly control on livestock. Under a special local needs (SLN) registration, pirimiphos-methyl is used to control mealy bugs on iris bulbs via fumigation in a single propagation nursery in Washington State.



Pirimiphos-methyl

Products containing pirimiphos-methyl are formulated into liquid concentrates, ready-to-use solutions and treated articles (ear tags). Based on uses supported through reregistration, human health risk is associated with potential exposure to pirimiphos-methyl through consumption of treated crops and livestock commodities, and in occupational settings. The HED Metabolism Assessment Review Committee (MARC) has determined that the residues of concern in stored grain and livestock commodities include pirimiphos-methyl and its des-ethyl metabolite. However, in order to harmonize with CODEX, only the parent, pirimiphos-methyl, is included in the revised tolerance expression [40 CFR §180.409]. Dietary exposure to both the parent and the des-ethyl metabolite has been included in dietary risk assessments conducted for pirimiphos-methyl.

HED has previously completed a preliminary human health risk assessment for pirimiphos methyl (C. Swartz, 10/23/98). The registrant has commented on this risk assessment, which is based on human toxicity studies for dose and endpoint selection. The Agency is currently undergoing reconsideration of its policy on using human toxicity studies, so the Hazard Identification Assessment Review Committee (HIARC) has selected animal toxicity studies for use in risk assessments in the interim. HED scientists have completed the following documents since the 10/23/98 risk assessment:

- Report of the Hazard Identification Assessment Review Committee: J. Rowland and P. Wagner, 5/26/99 (Attachment 1);
- The ORE aspects of the HED Chapter of the RED: S. Hanley, 6/1/99 (Attachment 2);
- Acute and Chronic Dietary Exposure/Risk Analyses: Christina Swartz, 7/13/99 (Attachment 3); and
- Anticipated Residue Assessment: Christina Swartz, 7/7/99 (Attachment 4).

HED has recently clarified the policy regarding the inclusion of the Food Quality Protection Act (FQPA) uncertainty factor in the Reference Dose, or RfD. The Population Adjusted Dose (PAD) is a modification of the acute RfD or chronic RfD to include the FQPA Safety Factor. The PAD is equal to the acute or chronic RfD divided by the FQPA Safety Factor. The dietary exposure risk estimate is now expressed as a percentage of the PAD, instead of the RfD as in the previous

version. The aPAD refers to the acute population dose and the cPAD refers to the chronic population adjusted dose.

SUMMARY/CONCLUSIONS

Highly refined acute and chronic dietary risk assessments for pirimiphos methyl generally result in risks that are below the Agency level of concern. Monitoring data from the USDA Pesticide Data Program (PDP) were used for high fructose corn syrup and from FDA for corn grain. Controlled magnitude of residue studies combined with usage data were used for other commodities. The apparent chronic dietary risk could be reduced even further if the outstanding toxicology data gaps for chronic studies were fulfilled (refer to the Detailed Considerations). Additional usage data for popcorn would also refine the acute and chronic dietary risk estimates. An aggregate exposure/risk assessment (i.e., including residential exposure and dietary exposure through drinking water) is not applicable, based on registered use patterns for pirimiphos-methyl.

Data summarized in a 10/97 report, "Evaluation of Pirimiphos-methyl: Evaluation of Use in Agriculture, Horticulture, Food Storage Practice and Home Gardens," completed by the UK Ministry of Agriculture, Fisheries and Food (MAFF), indicate there is likely to be some dietary risk associated with imported commodities treated with pirimiphos-methyl. Although the UK monitoring data are not adequate to quantify dietary risk using from imported commodities, the data suggest that residues in imported commodities are generally low or below the limit of detection. FDA monitoring data for numerous imported fruits and vegetables also showed non-detectable residues. Dietary risk from imported commodities has not been included in the human health risk assessment completed by HED as the exposure is expected to be minimal.

Short-term and intermediate-term occupational exposure and concomitant risk associated with mixing, loading and applying products containing pirimiphos-methyl for bin disinfestation and top-dress treatments exceed the Agency's level of concern. Due to a lack of chemical-specific data, occupational exposure/risk assessment for handlers was accomplished using data of varying quality from the Pesticide Handlers Exposure Database (PHED), label information (i.e., for iris bulb fogging), and cultural practices information.

The Margins of Exposure (MOEs) exceeding the level of concern for short- and intermediate-term exposure represent the maximum level of mitigation through additional personal protective equipment (PPE) and engineering controls currently applied in HED. Occupational risk for handlers could be refined via submission of additional information such as typical application rates, the amount of grain handled, data pertaining to dermal absorption, and chemical- or scenario-specific data.

DATA REQUIREMENTS

Additional data requirements have been identified in the science chapters (see attachments).

Toxicology:

The following studies must be submitted (OPPTS Test Guideline Nos. indicated in parentheses):

Chronic toxicity study in dogs (870.4100); and
Combined chronic toxicity/carcinogenicity study in rats (870.4300).

Product and Residue Chemistry:

Registered labels should be amended to remove the uses on rice and wheat “for export only.” The use on bulk/bagged seed should be removed from registered labels pending satisfaction of OPPTS 860.1500 (see below). Note that HED has recommended a revision in the tolerance expression to include only residues of the parent pirimiphos-methyl *per se*. Data are required as follows:

OPPTS Guideline No. 830.7050: UV/Visible absorption data;
OPPTS Guideline No. 860.1380: Storage stability data to support residue trials on grain;
and
OPPTS Guideline No. 860.1500: Magnitude of the residue in forage/stover grown from treated bulk/bagged seed.

Occupational Exposure:

Label language referring to personal protective equipment (PPE) and engineering control use must be altered to reflect the basis of the current occupational exposure/risk assessment. For example, for admixture and bulk/bagged seed treatments, the HED assessment is based solely on the use of closed systems; labels must be revised to prohibit use of open systems. For the fogging use on iris bulbs in Washington State, the label must be amended to reflect concerns over entry into previously fogged areas and to require glove use at planting. Site-specific incident data and health and safety programs of the company that makes the applications should be provided for the iris bulb fogging use. For scenarios which exceed HED’s level of concern for intermediate-term risk, additional mitigation measures are required.

Scenario-specific exposure data and additional cultural practices information could be used to refine the Agency’s risk assessment for occupational handlers.

DETAILED CONSIDERATIONS

TOXICOLOGY

The toxicology database for pirimiphos-methyl is not complete, but can be used for human health risk assessments. The available toxicology data show that pirimiphos-methyl inhibits cholinesterase activity in various species, including humans, rabbits, guinea pigs, rats and mice. Pirimiphos-methyl causes dose-related inhibition in plasma, red blood cell (RBC) and brain cholinesterase (ChE) activity by all routes of exposure and following exposure for various durations. Clinical symptoms associated with exposure to pirimiphos-methyl include tremors, ataxia, leg paralysis, abnormal gait and salivation. However, none of the animal studies submitted to EPA indicate changes in brain weight or histopathology. Cholinesterase inhibition occurs at very low dose levels, and is reversible when exposure is discontinued. Pirimiphos-methyl has relatively low acute oral, dermal and inhalation toxicity; both eye and skin irritation was observed in rabbits (Table 1). The HIARC concluded that the chronic/carcinogenicity studies submitted to EPA are not adequate to determine the carcinogenic potential of pirimiphos-methyl; however, acceptable mutagenicity studies indicate no genotoxicity concerns.

Table 1. Acute Toxicity Profile

OPPTS GDLN	MRID	Study Type	Species	Results	Tox Category
870.1100	00126257	Acute Oral	rat	LD ₅₀ = 2.4 g/kg	III
870.1200	00126257	Acute Dermal	rabbit	LD ₅₀ = >3.5 g/Kg for females and between 2.2-3.5 g/Kg for males	III
870.1300	41556304	Acute Inhalation	rat	LC ₅₀ = >4.7 mg/L	IV
870.2400	00126257	Primary Eye Irritation	rabbit	Irritant	II
870.2500	00126257	Primary Skin Irritation	rabbit	Moderate Irritant	III
870.2600	00126257	Dermal Sensitization	guinea pig	Non-sensitizer	N/A

N/A = Not applied; * With the exception of this study, all other acute toxicity studies were conducted on the 75% formulation of pirimiphos-methyl.

TOXICITY ENDPOINTS

The toxicological endpoints for risk assessment are summarized in Table 2 at the end of this section. Details of the studies selected as a basis for the endpoints are presented in Attachment 1 (HIARC document) and are summarized below. Previous risk assessments for pirimiphos-methyl are based on endpoints selected from two human toxicity studies. The Agency is currently developing a policy on utilizing studies employing human subjects for testing pesticides. In the interim the Agency has selected animal toxicity studies to be used in the human risk assessment. When considering the decisions on endpoints, doses, and uncertainty factors, the Hazard Identification Assessment Review Committee (HIARC) considered the relative Lowest Observed Adverse Effect Levels (LOAELs) found in the human and animal studies and study design.

It should be noted there are considerable deficiencies in the two human studies, so they are useful only as supplemental data. Although the 28-day study in humans (Chart *et al.* 1974) is not appropriate for use in risk assessment, it did provide some evidence that humans may be more sensitive than animals since the effect level for cholinesterase inhibition in humans (0.25 mg/kg) is lower than the effect levels seen in repeated dose animal studies. In addition, the 28-day human study tested only a single dose in five male subjects and, although plasma and red blood cell cholinesterase activity were measured, the time of sampling varied from subject to subject. These types of data, while providing a qualitative snapshot of time course vs. cholinesterase inhibition, are inadequate for quantitative purposes. Although the 56-day study in humans (Howard *et al.* 1976) used male and female subjects and provided supportive scientific data, it is not appropriate for use in risk assessment since it only included a single dose (thus no dose-response data) and did not measure cholinesterase activity in all subjects. Additionally, steady-state was not achieved and the treatment regimen (56 days) is not adequate to characterize lifetime exposure. Therefore, no comparison of a dose and effects in animals and human subjects could be made.

Acute Dietary Endpoint for Risk Assessment

The acute dietary endpoint was selected from an acute neurotoxicity study in the rat (MRID No. 43594101). Test groups of Sprague-Dawley rats (17/sex/dose) received a single oral administration of pirimiphos methyl in corn oil at 0, 15, 150 or 1500 mg/kg. After 24 hours, plasma cholinesterase inhibition (ChEI) was observed in both sexes in rats dosed at 15 mg/kg/day, the lowest dose tested. Brain and red blood cell (RBC) ChEI was observed in males at this dose level as well. At the highest dose tested brain ChEI was observed for two weeks after the single dose. Alterations in motor activity and the functional observational battery (FOB) were found in the highest dose group as well.

The dose/endpoint/study is appropriate for this risk assessment because the effects were seen after a single exposure on Day 1. The uncertainty factor (UF) includes the 10x for intra-species variation, 10x for inter-species extrapolation, and 10x for the use of the Lowest Observed Adverse Effects Level (LOAEL) as well as the severity of effects (marked plasma as well as RBC and brain ChEI) seen at the lowest dose tested.

The acute reference dose (RfD) is 0.015 mg/kg/day. The acute population adjusted dose is 0.005 mg/kg/day.

Chronic Dietary Endpoint for Risk Assessment

The chronic dietary endpoint was selected from a subchronic neurotoxicity study conducted in the rat (MRID No. 43608201). Test groups of Sprague-Dawley rats were fed diets containing pirimiphos-methyl (89.8%) at dose levels of 0, 0.2, 2.1 or 21.1 mg/kg/day for males and 0, 0.2, 2.4 or 24.7 mg/kg/day for females, respectively for 90-days. Plasma cholinesterase inhibition (ChEI) was observed in all test groups. The No Observed Adverse Effects Level (NOAEL) for brain and RBC ChEI was 2.1 mg/kg/day.

Longer-term studies reflecting exposure to the test material for a year or more are typically used to set the endpoint on which chronic risk assessments are based. However, no adequate chronic studies are available. Therefore the sub-chronic study, reflecting 90-day exposure, was used for the chronic risk assessment. Use of the study is supported by other longer-term studies, the two-generation reproduction study in rats and the carcinogenicity study in mice, in which the endpoint selected, cholinesterase inhibition, was observed at Weeks 3, 7, and 13. The uncertainty factor includes a 10x for intra-species variation, 10x for inter-species extrapolation, and 10x for the use of LOAEL and data gaps for long-term studies.

The chronic reference dose (RfD) is 0.0002 mg/kg/day. The chronic population adjusted dose is 0.00007 mg/kg/day.

Dermal and Inhalation Endpoints for Occupational Risk Assessment

Since endpoints were selected from oral studies, dermal and inhalation absorption rates, both assumed to be 100%, are applied to dermal and inhalation exposures in assessing risk associated with these exposures. Comparison of the acute oral and acute dermal LD₅₀ from studies conducted in rats and rabbits indicates that the assumption of 100% dermal absorption (relative to oral absorption) is not likely to be conservative.

Short-term dermal and inhalation exposure

The acute neurotoxicity study used to select the endpoint for the acute dietary assessment was used for the short-term dermal and inhalation assessment as well. Please refer to the previous section for a description of the study. The HIARC determined that a MOE of 1000 is required for occupational (there are no residential uses) exposure risk assessments. This includes the conventional UF of 100 and an additional UF of 10 for the use of the use of a LOAEL as well as severity of the effects (marked plasma, RBC and brain cholinesterase inhibition observed at the lowest dose tested).

Intermediate-term dermal and inhalation exposure

The sub-chronic neurotoxicity study used to select the endpoint for the chronic dietary assessment

was used for the intermediate-term dermal and inhalation assessment as well. Please refer to the previous section for a description of the study. The HIARC determined that a MOE of 300 is required for occupational (there are no residential uses) exposure risk assessments. This includes the conventional 100 and 3x for the use of a LOAEL.

Long-term dermal and inhalation exposure

The sub-chronic neurotoxicity study used to select the endpoint for the chronic dietary assessment was used for the intermediate-term dermal and inhalation assessment as well. Long-term exposure as a result of occupational use of pirimiphos-methyl products is not expected based on the currently-labeled use patterns. This endpoint was selected should future registrations result in long-term occupational or residential exposure.

Assessment for Special Sensitivity to Children and FQPA Safety Factor

Studies submitted to EPA indicate that younger rats are equally susceptible to ChE inhibition as older rats, and there appears to be no increase in sensitivity among fetuses or pups following pre- and/or post-natal exposure. However, the additional uncertainty factor required by FQPA was retained at 3X, since the data are not adequate to evaluate neurotoxicity following acute and long-term exposure, or to assess the functional development of young animals and in turn the susceptibility to infants and children. Insufficient data are available to assess the need for a developmental neurotoxicity study.

Table 2. Toxicological Endpoints for Risk Assessment ¹

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE
Acute Dietary	LOAEL=15 UF = 1000	Marked plasma, RBC and brain cholinesterase inhibition at the lowest dose tested	Acute Neurotoxicity-Rat Study	Not Relevant
	Acute RfD =0.015 mg/kg/day FQPA Acute Population Adjusted Dose (aPAD) = 0.005 mg/kg/day ²			
Chronic Dietary	LOAEL=0.2 UF= 1000	Plasma cholinesterase inhibition in both sexes at the lowest dose tested.	Subchronic-Rat	Not Relevant
	Chronic RfD =0.0002 mg/kg/day FQPA Chronic Population Adjusted Dose (cPAD) = 0.00007 mg/kg/day ²			
Dermal Absorption	100%, based upon the comparisons of LOAELs in the oral developmental toxicity (24 mg/kg/day) and the 21-day dermal (4 mg/kg/day) toxicity studies in rabbits based on the common endpoint (cholinesterase inhibition)			
Short-Term (Dermal & Inhalation) ³	Oral LOAEL=15	Marked plasma, RBC and brain cholinesterase inhibition at the lowest dose tested	Acute Neurotoxicity-Rat Study	1000 ⁴
Intermediate-Term (Dermal & Inhalation) ³	Oral LOAEL=0.2	Plasma cholinesterase inhibition in both sexes at the lowest dose tested.	Subchronic-Rat	300 ⁵
Long-Term (Dermal & Inhalation) ³	Oral LOAEL=0.2	Plasma cholinesterase inhibition in both sexes at the lowest dose tested.	Subchronic-Rat	300 ⁵

¹ NOAEL = No Observed Adverse Effect Level; LOAEL = Lowest Observed Adverse Effect Level; ChE = Cholinesterase

² Population Adjusted Dose (PAD) = RfD/FQPA factor (for this chemical FQPA factor = 3x)

³ Oral values were selected, therefore route-to-route extrapolation is used (100% dermal and 100% inhalation absorption).

⁴ MOE of 1000 due to severity of the effects (marked plasma, RBC and brain ChEI at the LOAEL)

⁵ MOE of 300 due to the use of the LOAEL

AGGREGATE RISK

The FQPA of 1996 requires the Agency to consider aggregate exposure and concomitant risk in its decision-making process for dietary (food source and drinking water), residential, and other non-occupational exposures. Since there are no residential exposure scenarios associated with registered uses of pirimiphos-methyl, and since no dietary exposure is expected through drinking water (L. Parsons memo dated 1/13/98), dietary risk is the only component of the aggregate risk assessment for the active ingredient pirimiphos-methyl.

DIETARY RISK

When conducting dietary risk analyses, the Agency begins by assuming that all commodities (that are being supported in reregistration) are treated and bear residues at the maximum legal limit, the tolerance. This represents a worst-case scenario and is an exaggeration of the actual risk. If the risk estimate is below the level of concern, then further refinement of the assessment is not necessary. Should the risk exceed the Agency level of concern, the dietary exposure assessment is refined by calculating expected residue levels in foods (instead of the legal maximum) and incorporating reliable information on the percentage of crop treated with the pesticide.

Acute and chronic dietary risk analyses were conducted using the Dietary Exposure Evaluation Model (DEEM™). The DEEM™ software estimates chronic dietary exposure to pesticides in foods based on the 3-day average of consumption data collected in USDA's Continuing Surveys of Food Intake by Individuals, 1989-1992. Acute dietary exposure is based on the distribution of consumption found in the same surveys. Probabilistic acute analyses were also conducted using distributions of consumption and distribution of residue levels from residue monitoring data. Dietary risk is expressed as a function of dose through dietary exposure. The Agency generally assumes that a risk less than 100% of the population-adjusted dose (PAD) is protective of the public health.

Several assessments were conducted for pirimiphos-methyl and are presented in Table 3 for chronic exposure and in Table 4 for single-day or acute exposure. The initial analyses of the acute and chronic dietary risk, assuming tolerance level residues (at the recommended reassessment level) and 100% crop treated, resulted in risks that greatly exceeded the level of concern. The anticipated residues used in the 10/98 assessment were revised to include new monitoring data and a revised analysis of pirimiphos-methyl usage (A. Halvorson, 4/8/99). FDA monitoring data were directly used for food corn and corn bran, which represents corn flour, corn meal, and other similar products. These data were also used for corn oil with an adjustment for reduction of residues when processed to food-grade oil. Residues of pirimiphos-methyl were not detectable in most samples. USDA Pesticide Data Program (PDP) monitoring data for high-fructose corn syrup showed non-detectable residues for every sample and were used for corn syrup and corn molasses. Magnitude of residue studies were used for sorghum grain.

The anticipated residues for popcorn were calculated four different ways. BEAD estimated the

percent crop treated for corn as <1%, with no separate distinction for popcorn. (It should be noted that popcorn does not expressly appear on the product label, only corn.) Out of 70 samples analyzed for residues of pirimiphos methyl over the past 7 years, FDA had a detection rate of 34% in popcorn. A somewhat higher detection rate (than percent crop treated) would be expected since there is likely to be blending of untreated popcorn with treated, which would result in residue levels in the blended commodity that would be lower than those found in the residue trials, where there is no blending. Average residue levels in the monitoring samples were lower than the average from residue trials (2.5 vs. 1.4 ppm), but not as much as expected. FDA data for popcorn could not be used directly since the Agency typically requires a minimum of 100 monitoring samples.

Assessment 1, the least conservative analysis, which could possibly underestimate the risk, assumes average residues from magnitude of residue trials and <1% crop treated. The remaining three analyses are increasingly conservative in the assumptions. The second assessment uses the same residue value, but assumes 34% crop treated (based on the rate of detection in the FDA monitoring samples). No adjustments for percent crop treated were made in the remaining two assessments. Assessment 3 uses the average value of the detects in the FDA monitoring data as the residue value, and Assessment 4 uses the average value from the corn grain residue trials.

The most highly exposed population sub-groups after refinement of residues Children 1-6 years and Children 7-12 years. The most conservative refined assessment, which the Agency believes is an overestimate, resulted in a risk that exceeded 100% of the population adjusted dose for both the acute and chronic analyses. The risk was below the level of concern in the other three refined assessments for all population sub-groups. As a result, the Agency does not have a risk concern from dietary exposure to pirimiphos-methyl.

To further characterize dietary exposure/risk, the Agency generated an acute critical exposure contribution analysis and a chronic commodity contribution analysis for the worst-case scenario, Assessment 4. These analyses indicate that at the 99.9th percentile of exposure, both popcorn and corn grain are significant contributors to the estimated acute dietary risk, but estimated chronic dietary risk is almost entirely due to residues in popcorn. The highest detected residue in the corn grain FDA monitoring data appears to have a greater impact on the estimated acute exposure and risk at the 99.9th percentile than excessive consumption events for individual survey respondents. Additional usage data for popcorn would help to further refine the risk assessment. It should be noted that heating and popping data are not available, which would further refine the assessment as well.

Table 3. Pirimiphos-methyl Chronic Dietary Exposure and Risk Estimates¹

Population Subgroup	Chronic Reassessed Tolerances 1		Chronic Reassessed Tolerances 2		Chronic ARs Refined Assessment 1		Chronic ARs Refined Assessment 2		Chronic ARs Refined Assessment 3		Chronic ARs Refined Assessment 4	
	Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	%cPAD	Exposure (mg/kg/day)	%cPAD	Exposure (mg/kg/day)	%cPAD	Exposure (mg/kg/day)	%cPAD	Exposure (mg/kg/day)	%cPAD
General U.S. Population	0.006150	9200	0.000740	1,100	0.000002	2.9	0.000021	32	0.000035	52	0.000060	90
All infants (<1 yr)	0.075708	23,400	0.000328	490	0.000002	2.3	0.000002	2.3	0.000002	2.3	0.000002	2.3
Nursing infants (<1 yr)	0.003917	5800	0.000068	100	0.000000	<1	0.000000	<1	0.000000	<1	0.000000	<1
Non-nursing infants (<1 yr)	0.020671	30,900	0.000438	650	0.000002	3.1	0.000002	3.1	0.000002	3.1	0.000002	3.1
Children (1-6 years)	0.014246	21,300	0.001548	2,300	0.000004	5.9	0.000034	51	0.000055	82	0.000094	141
Children (7-12 years)	0.010967	16,400	0.001256	1,900	0.000003	4.8	0.000032	48	0.000052	77	0.000090	134
Females (13-19)	0.006245	9,300	0.000735	1,100	0.000002	2.8	0.000019	29	0.000031	47	0.000054	81
Females (20+ years)	0.003883	5,800	0.000497	740	0.000001	2.0	0.000019	28	0.000030	45	0.000053	79
Females (13-50 years)	0.004582	6,800	0.000568	850	0.000002	2.3	0.000021	31	0.000034	51	0.000060	89
Males (13-19 years)	0.007982	11,900	0.000853	1,300	0.000002	3.4	0.000027	41	0.000044	66	0.000077	115
Males (20+ years)	0.004335	6,500	0.000640	960	0.000002	2.4	0.000018	27	0.000030	44	0.000052	77
Description of Assessment	Tolerance level residues and 100%CT ² for all commodities		Tolerance level residues and 100%CT ² for most commodities; excludes HFCS and sugar/molasses.		Used anticipated residues for most commodities; assumed <1%CT and average residue trial values for popcorn.		Used anticipated residues for most commodities; assumed 34%CT and average residue trial values for popcorn.		Used anticipated residues for most commodities; used average of FDA monitoring detects, and no adjustment for %CT.		Used anticipated residues for most commodities; used average residue trial value, and no adjustment for %CT.	

¹ The chronic PAD (cPAD) is 0.000067 mg/kg/day.

² %CT = Percent crop treated.

Table 4. Pirimiphos-methyl: Probabilistic Acute Dietary Exposure and Risk Estimates¹

	Deterministic Analysis (95th Percentile of Exposure Reported)				Probabilistic Analysis (99.9th Percentile of Exposure Reported)							
Population Subgroup	Acute Reassessed Tolerances 1		Acute Reassessed Tolerances 2		Acute ARs Refined Assessment 1		Acute ARs Refined Assessment 2		Acute ARs Refined Assessment 3		Acute ARs Refined Assessment 4	
	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD	Exposure (mg/kg/day)	%aPAD
General U.S. Population	0.019524	390	0.003348	67	0.002559	51	0.002678	54	0.003102	62	0.004591	92
All infants (<1 yr)	0.049357	990	0.002008	40	0.002664	53	0.002664	53	0.002664	53	0.002664	53
Nursing infants (<1 yr)	0.016215	320	0.000654	13	0.000584	12	0.000584	12	0.000584	12	0.000584	12
Non-nursing infants (<1 yr)	0.052105	1,000	0.002208	44	0.002884	58	0.002884	58	0.002884	58	0.002884	58
Children (1-6 years)	0.037433	750	0.005705	114	0.004017	80	0.004168	83	0.004774	95	0.007040	141
Children (7-12 years)	0.027216	540	0.005140	103	0.003158	63	0.003214	64	0.003415	68	0.005029	101
Females (13-19)	0.016340	330	0.003201	64	0.002684	54	0.002698	54	0.002701	54	0.003549	71
Females (20+ years)	0.011013	220	0.002332	47	0.001568	31	0.001773	35	0.002185	44	0.003563	71
Females (13-50 years)	0.013017	260	0.002671	53	0.001786	36	0.001990	40	0.002531	51	0.003755	75
Males (13-19 years)	0.019612	390	0.003721	74	0.002225	44	0.002314	46	0.002749	55	0.004309	86
Males (20+ years)	0.012203	240	0.002768	55	0.002121	42	0.002192	44	0.002471	49	0.003645	73
Description of Assessment	Tolerance level residues and 100%CT ² for all commodities		Tolerance level residues and 100%CT ² for most commodities; excludes HFCS and sugar/molasses.		Used anticipated residues for most commodities; assumed <1%CT and average residue trial values for popcorn.		Used anticipated residues for most commodities; assumed 34%CT and average residue trial values for popcorn.		Used anticipated residues for most commodities; used average of FDA monitoring detects, and no adjustment for %CT.		Used anticipated residues for most commodities; used average residue trial value, and no adjustment for %CT.	

A 10/97 study entitled “Evaluation of Pirimiphos-methyl: Evaluation of Use in Agriculture, Horticulture, Food Storage Practice and Home Gardens,” completed by the UK Ministry of Agriculture, Fisheries and Food (MAFF) was submitted to EPA [no MRID #, DP Barcode No. D241203]. The study report summarizes use patterns and residue data for commodities grown outside the US. The uses covered include applications to apples (France, UK); plums, strawberries, black currants, carrots, onions, peppers, cauliflower, peas (seeds and whole pods), green beans, celery, potatoes and raspberries (UK); tomatoes (West Germany, UK and Holland); cucumbers, cabbages and lettuce (West Germany and UK); and Brussels sprouts (UK and Holland).

Conclusions of the MAFF regarding the nature and magnitude of the residue in stored grain are in general agreement with the conclusions summarized in HED documents. MAFF has followed the Codex policy of including only residues of pirimiphos-methyl *per se* in risk assessments. Metabolism data summarized in the MAFF report indicate that the des-ethyl metabolite comprises a maximum of 10% of the residue in treated crops. Average residues in the commodities listed above, based on field trial studies conducted in the countries listed, were summarized in the MAFF report. For most commodities, average residues ranged from a minimum of non-detectable (<0.01 ppm) to < 1 ppm. However, residues of up to 2 and 8 ppm were reported in Brussels sprouts and celery, respectively. There were no data available to assess registered uses on mushroom, broccoli, calabrese and wheat, and on pears grown in Northern Europe. The allowable daily intake (ADI) reported in the MAFF document is 0.03 mg/kg/day, taken from a human study in which cholinesterase inhibition was selected as the endpoint; the report did not indicate if the ADI is for acute or chronic exposures in the diet.

Monitoring data generated by the UK Working Party on Pesticide Residues (WPPR) were also summarized in the MAFF report. In general, less than 100 samples were taken for each commodity; both imported (to the UK from other countries) and UK-grown commodities were sampled. The commodities included aubergine (eggplant); carrot; chili peppers; kiwi fruit; orange; sweet pepper; bran; biscuits; white rice (short and long grain); brown rice (long grain); buckwheat; millet; rye; bread crumbs; bread (wholemeal, white, multi grain, and brown); “organic” bread (wholemeal, brown, and white); malt extract (with and without fish oil); beef; lamb; cattle, sheep and pig kidney fat; and evening primrose oil.

Pirimiphos-methyl residues were detected in 7/23 kiwi samples (0.05-0.3 ppm); 2/91 orange samples (0.07, 0.1 ppm); 1/15 sweet pepper samples (0.2 ppm); 30/46 bran samples (0.05-0.6 ppm); 14/183 biscuit samples (0.05-0.1 ppm); 1/105 rice samples (0.05 ppm); 1/12 bread crumb samples (0.05 ppm); 2/37 wholemeal bread samples (0.07, 0.1 ppm); 1/25 brown bread samples (0.06 ppm); 1/37 white bread samples (0.06 ppm); 2/33 multi grain bread samples (0.05 ppm); 1/8 “organic” brown bread samples (0.08 ppm); and 1/4 samples of malt extract, without fish oil samples (0.07 ppm). Other commodities sampled, including all the livestock commodities, had no residues detected (<0.05 ppm).

Due to concerns regarding the potential for higher residues in single serving carrots, the MAFF

limited the maximum number of applications to carrots, and continued to monitor residues in both composite and single serving samples of carrots. Reductions in the residues detected were observed, but the MAFF determined that “some erosion of safety margins for consumers still existed.” Therefore, the restriction on the maximum number of applications to carrots has been retained, and the WPPR continues to monitor residues in carrots.

The UK report suggests that there is likely to be some dietary risk associated with pirimiphos-methyl uses in other countries. It is not possible to quantify the risk using the available information; however, the UK monitoring data suggest that residues are generally low or near the limit of detection.

FDA has monitored many imported commodities for residues of pirimiphos-methyl over the past several years. Residues have not been detected in any of these samples. The Agency generally believes that the exposure to pirimiphos-methyl from imported fruits and vegetables is minimal and was therefore not specifically included in the risk assessment.

OCCUPATIONAL RISK

No additional occupational exposure data were submitted after the preliminary assessment (10/98). Examination of use patterns on registered labels indicates exposure is expected to occur in the course of typical activities for occupational workers; exposure assessments have been completed for occupational handler and post-application scenarios. There are no products registered at this time for residential use. Short-term and intermediate-term occupational exposure assessments were conducted, but chronic occupational exposure scenarios are not expected to occur, based on use patterns supported through reregistration.

For occupational handlers, six scenarios served as the basis for the exposure/risk assessment. The registrant intends to propose a pour-on treatment for livestock (scenarios 4a and 4b in the ORE Chapter). The pour-on use was incorporated into the assessment dated 6/1/99, but is not included in the HED risk assessment for reregistration since it is not a registered use, and since it has not formally been submitted to the Agency. The potential for post-application exposure is expected only in conjunction with the fogging use on iris bulbs in Washington State; short-term inhalation exposure is of concern following this fogging operation. No other scenarios are expected to result in either dermal or inhalation post-application exposure.

Since there were no chemical-specific exposure data, unit exposures (dermal and inhalation) for occupational handler scenarios were derived from the Pesticide Handlers Exposure Database (PHED Surrogate Data Table, 5/97); several handler assessments were completed using “**low quality**” PHED data due to the lack of higher quality data. No data were available to assess exposure during application of ear tags to livestock. Several generic protection factors were used to calculate handler exposures, although protection factors for clothing layers have not been completely evaluated by HED. In calculating daily exposures, factors such as tons of grain

treated per day were based on best professional judgement due to a lack of pertinent data. Empirical data were not available for determining post-application inhalation exposure after greenhouse fogging, and therefore air exchange rates and anticipated chemical dissipation patterns were used to derive an exposure concentration for pirimiphos-methyl.

For short-term exposure to pirimiphos-methyl, a margin of exposure (MOE) of 1000 is considered to be protective, while an MOE of 300 is considered protective for intermediate-term occupational exposure. (For details on the selection of the appropriate MOE levels, see p. 8, Summary of Toxicity and Endpoint Selection.) A summary of occupational scenarios and associated risks assuming the baseline clothing scenario, protective clothing and PPE (personal protective equipment), and engineering controls is presented in Table 5. Shaded regions in the table indicate scenarios for which occupational exposure exceeds the Agency's level of concern for short-term and intermediate-term risk. HED notes that for some scenarios with unacceptable MOEs (mixing/loading/applying for bin disinfestation or topdress treatment), further mitigation of risk using engineering controls is not feasible, due to the type of equipment involved. These scenarios include applications using either a high pressure hand-wand or backpack sprayer, for which engineering controls typically do not exist.

HED is particularly concerned with the potential for intermediate-term risk to occupational workers mixing, loading and applying products containing pirimiphos-methyl for bin disinfestation and top-dress treatment. The intermediate-term MOEs exceeded the Agency's level of concern even though protection factors were applied to adjust exposure for additional clothing, personal protective equipment (PPE). The MOEs for short-term risks also exceeded the level of concern for the top-dress scenarios (MOEs were less than 1000), with the exception of workers wearing maximum personal protective equipment and applying liquids with a low-pressure handwand. Short-term risks for workers applying pirimiphos-methyl as a top-dress treatment exceeded the level of concern by a slight margin.

The fogging treatment for iris bulbs scenario is a very limited use that is atypical of most applications. The 24 (c) registration is currently used at a single propagation nursery in the state of Washington. Although the label does not specify personal protective equipment (PPE), in two letters to the Agency, commercial applicators have state that new Tyvek coveralls, rubber gloves, and Self-Contained Breathing Apparatus (SCBA) are all used to protect applicators.

No data were available to the Agency to assess the occupational risk of workers conducting the iris bulb fogging treatment. Therefore, an alternative method, consistent with industrial hygiene approaches, was used to consider these exposures to ensure that the individuals involved are adequately protected. The fogging application rate (not accounting for any dilution) results in an airborne concentration of 3.63 mg/L. If the NIOSH protection factor for a tight-fitting SCBA is applied to this value the resulting exposure concentration is 0.00036 mg/L which is 5 orders of magnitude less than the acute inhalation toxicity concentration of 5.04 mg/L. Standard industrial hygiene practices for similar situations recommend at least three orders of magnitude difference. Dermal exposures are not the primary concern for this application scenario considering the use of Tyvek coveralls and gloves.

Table 5. Summary of Occupational Risk for Pirimiphos-methyl¹

Exposure Scenario	Baseline Clothing ²		Protective Clothing/PPE ³		Engineering Controls ⁴	
	Short-Term Risk (MOE)	Intermediate-Term Risk (MOE)	Short-Term Risk (MOE)	Intermediate-Term Risk (MOE)	Short-Term Risk (MOE)	Intermediate-Term Risk (MOE)
Mixer/Loaders						
Mixing/loading Liquids For Admixture Grain Treatment	Not feasible, since only closed loading system (considered to be an engineering control) are being supported in re-registration.				17,000 (min rate) 14,000 (max rate)	240 (min rate) 180 (max rate)
Mixing/loading Liquids For Seed Treatment					68,000	910
Loading Liquids For Fogging Treatment of Iris Bulbs	13	<1	2100	27	N/F	N/F
Applicators						
Fogging Treatment of Iris Bulbs	Not Feasible - See text					
Cattle Ear Tags	No Data	No Data	No Data	No Data	N/F	N/F
Mixer/Loader/Applicator						
Mixing/loading and Applying Liquids [Top dress]	15	<1	4,200	55	Not feasible; no engineering controls have been identified for these occupational scenarios.	
Using a Low Pressure Handwand [Bin Disinfestation]	8	<1	3,200	30		
Mixing/loading and Applying Liquids [Top dress]	600	8	940	13		
Using a Backpack Sprayer [Bin Disinfestation]	330	4	500	7		
Mixing/loading and Applying Liquids [Top dress]	580	8	940	13		
Using a High Pressure Handwand [Bin Disinfestation]	310	4	500	7		

¹ Only occupational risk is summarized, since there are no residential exposure patterns based on the registered uses. The data are summarized from the 6/1/99 ORE Chapter of the HED RED.

N/A = not applicable; N/F = Not Feasible (the assumption of either baseline clothing, additional PPE or engineering controls does not exist for the relevant scenario).

MOE = Margin of Exposure = NOAEL (or LOAEL)/exposure; MOEs of 1000 and 300 are considered to be protective for short-term and intermediate-term occupational exposures, respectively.

- ² The baseline clothing and PPE scenario consists of workers wearing a single layer of clothing, no gloves, and no respirator. Mixing/loading activities are open; open cab is assumed for applicators and flaggers.
- ³ Additional PPE scenarios consist of workers wearing a double layer of clothing, chemical resistant gloves and a respirator.
- ⁴ For engineering controls scenarios, it is assumed that workers wear a single layer of clothing and no gloves while using an appropriate engineering control system (i.e., closed mixing, enclosed cabs).